

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460



OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

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Dear Mr. Sussman:

This letter provides the Environmental Protection Agency's (EPA's) response, upon reconsideration, to a petition it received under section 21 of the Toxic Substances Control Act (TSCA) from the Center for Environmental Health, Cape Fear River Watch, Clean Cape Fear, Democracy Green, Toxic Free NC, and the NC Black Alliance (petitioners) on October 14, 2020. After reconsidering its prior January 2021 denial of the petition, EPA is granting the petition.

On October 14, 2020, petitioners submitted to EPA a petition under TSCA section 21 to initiate a rulemaking proceeding or issue an order under TSCA section 4(a)(1)(A)(i), compelling health and environmental effects testing regarding perfluoroalkyl and polyfluoroalkyl substances (PFAS). The petitioners requested such testing in connection with 54 chemical substances the petition identifies as PFAS and alleges are released into the environment by The Chemours Company (Chemours). As petitioners stated, the intent of the petition is to develop information that would enable the Cape Fear River watershed communities to better understand the potential effects to their health from PFAS exposures. The petitioners also included a detailed proposed testing program to further this goal. As part of the testing program petitioners put forth to achieve this goal, they suggested the Agency require:

- Testing on 54 chemical substances;^{1,2}
- Animal studies on three chemical mixtures;
- Human studies of communities exposed to PFAS from drinking water and other pathways, including residents from the Cape Fear River watershed;

¹ Although the petitioners refer to testing on 54 substances, the petitioners request testing on 55 unique chemical substances. Specifically, the petitioners refer to the GenX dimer acid (CAS No. 13252-13-6) and ammonium salt forms (CAS No. 62037-80-3) as a single substance, even though the petitioners use both CAS numbers at different points in the petition. For purposes of the response, the Agency will continue to refer to 54 chemical substances, as characterized in the petition.

² The proposed testing program for the substances included human health effects studies in experimental animals, physical and chemical property studies, fate and transport studies, and eco-toxicity testing. The Agency's response will address these studies generally as testing on the individual PFAS or 54 chemical substances.

- Human half-life studies on all 54 substances in Chemours' workers; and
- Development and submission of analytical standards.

The petitioners also suggested that EPA would contract with the National Academy of Sciences (now known as the National Academies of Sciences, Engineering, and Medicine [NASEM]) to create an independent science panel to oversee all aspects of the testing program suggested by the petitioners (Ref. 1).

Upon reconsideration, the Agency has determined to grant the petition under TSCA section 21 to issue a rule or order under TSCA section 4(a)(1)(A)(i) compelling health and environmental effects testing regarding PFAS. With respect to the petitioners' proposed testing program, and as described in greater detail below, EPA generally expects to take some immediate actions and to defer certain other actions pending the development of additional information that will inform future decision-making, in accordance with statutory requirements. The Agency's response also explains in greater detail below that a narrow subset of the recommendations of the petition fall outside the scope of TSCA section 21 and/or our statutory authority.

As a precursor to summarizing the Agency's planned actions in response to the grant of the petition, it is helpful to briefly note that EPA recently developed a National PFAS Testing Strategy (Testing Strategy) (Ref. 2). The Testing Strategy identifies priority categories with representative substances for testing that comprises the first of several described phases of an iterative testing approach based on grouping of chemicals by chemistry features. These categories include most of the chemicals identified in the petition, as well as additional PFAS, and the testing conducted will inform a wider universe of data-poor PFAS. This first phase of testing on 24 PFAS is expected to provide data that can be extrapolated to 2,950 PFAS that belong to the same categories as the 24 individual substances.

What follows is a summary of the Agency's current views with respect to the proposed testing program presented in the petition:

- **Near-Term Testing Covers 30 of 54 Petition Chemicals** – Under the testing strategy, EPA's first test orders for 24 data-poor categories of PFAS will provide data that cover 30 of the 54 petition chemicals. Seven orders will be issued specifically for petition chemicals, which are in categories that also include 14 additional PFAS identified in the petition. Four orders will be issued for non-petition chemicals, which are in categories that include nine additional PFAS identified in the petition. The initial test orders will include animal tests that measure most of the specific human health related toxicity endpoints identified as a concern by the petitioners (e.g., systemic, reproductive, developmental, thyroid, and immunological toxicity). Subsequent tiers of testing that will be specified in the initial test orders may include additional endpoints (e.g., cancer), depending on the results of the initial tiers of tests and consistent with the TSCA statutory requirement regarding tiered testing.
- **Subsequent Testing May Cover Nine of 54 Petition Chemicals** – An additional nine PFAS identified in the petition belong to one other category included in the Testing

Strategy. EPA is conducting more in-depth analyses of the sufficiency of the existing data, which will inform later phases of testing.

- **Remaining 15 of 54 Petition Chemicals** – Fifteen (15) chemicals identified in the petition do not fit the definition of PFAS used in developing the Testing Strategy. EPA has determined that there is robust data on some of them available to the Agency. EPA is conducting more in-depth analyses of the existing data, which will inform later phases of testing.
- **Mixtures Studies** – EPA is planning to address PFAS mixtures with component-based approaches wherein the toxicity of the product is determined or predicted from the toxicity of individual chemical substances that comprise the mixture, an approach which is consistent with the current state-of-science on PFAS. EPA is proceeding with development and peer review of such methods as specifically applied to PFAS.
- **Human Studies** – EPA is contributing to and reviewing numerous existing ongoing human studies, including studies on potentially exposed workers and communities in North Carolina, and is evaluating how to further advance and expand on these efforts.
- **Analytical Standards** – EPA does not believe it is appropriate to require the development or submission of analytical standards with the initial test orders that will be issued under the Testing Strategy and lacks the ability to order the submission of all analytical standards in the manner requested. Nonetheless, EPA has requested comment on whether to require the submission of existing analytical methods for PFAS under a separate rulemaking proceeding the Agency expects to finalize next year.

I. Background on the Section 21 Petition

A. Summary of the Petition History

EPA originally denied the petitioners' October 2020 request to initiate a rule or issue an order under TSCA section 4 on January 7, 2021. EPA's response was published in the Federal Register on January 22, 2021 (Ref. 3). That notice provided the basis for EPA's denial and concluded that the TSCA section 21 petition did not set forth the facts necessary for the Agency to make the required statutory determination that, for each of the 54 chemical substances, existing information and experience are insufficient and testing of such substance or mixture with respect to such effects is necessary to develop such information.

On March 4, 2021, the petitioners requested EPA reconsider its January 2021 denial and grant the petition (Ref. 4). Petitioners also filed a Complaint for Declaratory and Injunctive Relief in the Northern District of California to challenge the January 7, 2021, denial of the October 14, 2020, petition. EPA also received additional correspondence from the petitioners on March 16, 2021 (Ref. 5), restating their reconsideration request. EPA also received subsequent correspondence from the petitioners on April 12, June 4, July 28, and November 1 and 18, 2021 (Ref. 6, 7, 8, 9, 10).

After reviewing the request for reconsideration, EPA decided to grant the request for reconsideration and notified petitioners of its decision by letter on September 16, 2021 (Ref. 11). As a general matter, TSCA does not require EPA to revisit past decisions on TSCA section 21 petitions, and EPA does not anticipate undertaking such reconsiderations as a matter of course. The Agency's process for reviewing such petitions is robust and highly resource intensive, and the outcomes reflect careful consideration by expert career staff, counsel, and Agency leadership. EPA does, however, have inherent authority to reconsider past decisions and to revise, replace, or repeal a decision to the extent permitted by law and supported by a reasoned explanation. In this instance, EPA exercised its discretion to conduct another review of the petition denial so that it could fully explore and address the issues and concerns the petitioners raised in light of the change in administration and attendant change in policy priorities concerning PFAS.

B. Summary of the Petition

In support of their proposed testing program and their request for testing on the 54 chemical substances identified in the petition (see Table 1 of petition), petitioners allege that each of the substances meet the criteria in TSCA section 4(a)(1)(A) for requiring testing.

The petitioners assert that the 54 chemical substances may present an unreasonable risk of injury to health or the environment because “all PFAS have the potential for causing the adverse health and environmental effects linked to well-characterized substances like PFOS and PFOA” and there is exposure to each of the substances due to either their “presence in human blood, produce and/or drinking water” or their “presence in surface water, stormwater, wastewater, sediment, groundwater, soil, private wells, and/or air emissions.”

The petitioners also assert in the reconsideration request that, based on a literature search the petitioners conducted and provided a summary of, there is insufficient information on the chemical substances identified in the petition. The petitioners stated that their search included studies of physical-chemical properties, fate and transport, and ecotoxicity studies from the “EPA CompTox dashboard and the ECHA database.” For toxicity information, petitioners screened the EPA ChemView database and ToxValDB database. Finally, petitioners conducted a literature review of PubMed for each chemical to identify published toxicity studies not identified elsewhere (Ref. 4).

The petitioners also argue that the studies they propose are “the minimum necessary for a full understanding of the health risks from past present and future exposure to the 54 PFAS by petitioners.” The petition proposes the following tests on the substances: human health effects studies in experimental animals, physical and chemical property studies, fate and transport studies, and eco-toxicity testing.

The petitioners also suggest that formulation and testing of three mixtures is appropriate: a mixture of chemicals detected in the drinking water of Cape Fear communities downstream of the Chemours facility, a mixture of chemicals found in the blood of area residents during biomonitoring, and a mixture of chemicals from Chemours’ facility emissions and discharges. Petitioners suggest that the three mixtures undergo the “same set of animal studies” as the 54 individual chemicals identified in the petition. In support of this testing, petitioners assert that

studies on individual chemical substances do not account for the synergistic and additive effects of simultaneous exposure to multiple chemical substances and would likely underestimate health effects.

The petitioners also propose human studies of communities exposed to contaminated drinking water in the Cape Fear River watershed to understand medical histories of these individuals, examining chemical exposure indicators and health outcomes. The petitioners assert that studies in humans identify health effects associated with combined exposure to multiple substances and reflect those toxicokinetics and susceptibilities that are unique to humans, which the proposed rodent studies would not measure.

The petitioners also propose that the Agency require Chemours to conduct “longitudinal studies in its workers to detect the rate of increase and rate of decay of serum or tissue levels as exposure begins or ceases” for each of the “listed chemicals” in the petition. The petition asserts that the half-lives may vary between chemicals and that half-lives in humans may not be predicted from animal studies.

The petitioners propose that the Agency require that Chemours develop “valid analytical tools for detecting and measuring the presence” of the 54 chemical substances identified in the petition. The petition identifies EPA Method 860.1650, OPPTS Test Guideline for Submittal of Analytical Reference Standards, as an example.

C. Summary of the Statutory Requirements

TSCA section 21(a) authorizes any person to petition the Agency to “initiate a proceeding” for the issuance of a rule or an order under section 4. 15 U.S.C. § 2620(a).

TSCA section 21(b)(1) requires that the petition set forth the facts which petitioners claim establish that it is necessary to initiate the proceeding requested. 15 U.S.C. § 2620(b)(1). Thus, TSCA section 21 implicitly incorporates the statutory standards that apply to the requested actions. Accordingly, EPA has relied on the standards in TSCA section 21 and in the provisions under which actions have been requested in evaluating this TSCA section 21 petition.

TSCA section 4 imposes certain limitations on EPA’s authority to require testing and establishes requirements and considerations before EPA can require testing through a rule or order. These include:

1. Under TSCA section 4(a)(1)(A)(i), EPA must find that the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment; that information and experience are insufficient to reasonably determine or predict the effects of a chemical substance on health or the environment; and that testing of the chemical substance is necessary to develop the missing information. 15 U.S.C. § 2603(a)(1)(A)(i).

2. Under TSCA section 4(a)(4), EPA must employ a tiered screening and testing process, under which the results of screening-level tests or assessments of available information inform the decision as to whether one or more additional tests are necessary, unless information available to the Administrator justifies more advanced testing of potential health or environmental effects or potential exposure without first conducting screening-level testing. 15 U.S.C. § 2603(a)(4).
3. In the case of mixtures subject to testing under section 4(a)(1)(A), EPA must show that “the effects which the mixture’s manufacture, distribution in commerce, processing, use, or disposal or any combination of such activities may have on health or the environment may not be reasonably and more efficiently determined or predicted by testing the chemical substances which comprise the mixture.” 15 U.S.C. § 2603(a)(1)(B).
4. TSCA section 4(h) requires EPA to reduce and replace the use of vertebrate animals in the testing of chemical substances or mixtures. This includes a requirement under TSCA section 4(h)(1)(A) that, prior to requiring testing using vertebrate animals, the Agency must consider, as appropriate and to the extent practicable and scientifically justified, reasonably available existing information, including (i) toxicity information; (ii) computational toxicology and bioinformatics; and (iii) high-throughput screening methods and the prediction models of those methods. 15 U.S.C. § 2603(h)(1)(A).
5. Under TSCA section 4(h)(1)(B), EPA is also charged with encouraging and facilitating: (i) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under TSCA; (ii) the grouping of two or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category; and (iii) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests, provided that such consortia make all information from such testing available to the Administrator.

EPA is required under section 21 to respond to a petition within 90 days. TSCA section 21(b)(1) places the burden on the petitioners to present the facts that they claim establish that it is necessary for EPA to initiate the rule or issue the order sought. 15 U.S.C. § 2620(b)(1). Although the Agency may consider other relevant information that is reasonably available to the Agency during the 90-day petition review period, the period for consideration of the petition is limited and it is the petitioners’ burden, not the Agency’s, to provide facts demonstrating that the action sought is necessary. However, EPA retains discretion to determine what, if any, investigation or proceeding is appropriate prior to determining whether a petition should be granted or denied. See 15 U.S.C. § 2620(b)(2).

If a petition is denied, the Agency must publish the reasons for denial in the Federal Register. If a petition is granted, the statute instructs the Administrator to promptly commence an “appropriate proceeding” in accordance with sections 4, 5, 6, or 8 of TSCA. 15 U.S.C. § 2620(b)(3). The statute, however, does not dictate the precise timing of any EPA actions and EPA will decide on the details and scheduling during subsequent stages of the proceeding. EPA

also retains discretion to determine the content of any rules or orders that may be issued subsequent to a grant, which need not conform precisely to the petitioner's proposed action/s. Further, if EPA believes there are good reasons to defer action on the chemicals subject to a section 21 petition because the Agency has higher priority risks and insufficient resources, the Agency may grant the petition and commit to data gathering by informal or non-regulatory means, or to an extended schedule for action. Additionally, the action that constitutes "initiation" of an appropriate proceeding will vary depending on the circumstances of a particular case. A proceeding may be initiated by beginning a regulatory investigation, by holding public hearings, or by issuing an Advance Notice of Proposed Rulemaking. Further, initiating a proceeding in response to a section 21 petition does not commit EPA to subsequently take any specific type of action such as proposing a rule or to promulgating final regulations.

II. The Agency's Commitment to Take Action on PFAS

The Biden-Harris Administration shares petitioners' concerns regarding the potential risks posed by PFAS and has made a clear commitment to better understand and address those risks. The Agency also understands, and shares, petitioners' concerns about the historic and ongoing exposures to PFAS in the Cape Fear River watershed of North Carolina. The Agency's actions on PFAS, while generally national in scope, will accelerate efforts to understand PFAS exposures at a local level. In fact, petitioners' request that EPA leverage its authorities to compel development of much needed new information on PFAS underscored the need for robust testing on PFAS and played a key role in advancing the Agency's plans for a comprehensive testing strategy for PFAS.

The Agency has announced accelerated efforts to protect human health and the environment from PFAS. Subsequent to petitioners' request for reconsideration, in April 2021, EPA Administrator Regan directed the EPA Council on PFAS to work to develop a comprehensive, multi-year plan to ensure that EPA can deliver critical public health protections to the public through a dramatic enhancement of EPA's PFAS research, testing, monitoring and data collection, and regulatory efforts (Ref. 12). The PFAS Strategic Roadmap (Ref. 13), released on October 18, 2021, describes a whole-of-agency approach to addressing these issues, and reflects the Agency's leadership role in the national efforts to better understand PFAS and reduce risks. PFAS are – and will continue to be – a top priority for EPA.

Consistent with the objectives presented in the PFAS Strategic Roadmap, the EPA is leading a comprehensive portfolio of human health and environmental research, and development of methods, approaches, and information databases designed to advance decision-making associated with PFAS contamination across exposure matrices (e.g., water, soil, air). Considering that the vast majority of PFAS are 'data-poor', that is, lacking data that inform behavior in the environment or in exposed ecological or human populations, the EPA is investing significant resources into characterizing the chemical (i.e., structural, physicochemical) and toxicological (both kinetics and dynamics) properties of a diverse landscape of PFAS structures, in coordination with federal partners such as the National Institutes of Environmental Health Sciences (NIEHS). This includes computational modeling, a broad suite of in vitro testing methods and assays, and targeted ecological and mammalian bioassays. General objectives associated with this EPA PFAS research portfolio are: (1) to develop data that inform groupings of PFAS; (2) to identify PFAS that might serve as 'anchor' or 'index' chemicals within structural

groupings (i.e., well-characterized PFAS that can be leveraged to infer or interpolate to data-poor members of a grouping); (3) to populate selected data-poor PFAS with basic information pertaining to physicochemical and toxicological properties; (4) to fill data-gaps for PFAS with varying degrees of extant information (e.g., adverse outcome pathway; toxicity pathway-based metrics); and (5) to develop methods, approaches, assessments and/or frameworks for the evaluation of PFAS, including when occurring in mixtures.

III. Response to the TSCA Section 21 Petition

The Agency has reviewed the petition, reconsideration request, and subsequent letters submitted by petitioners and others, and has determined to grant the petition. Specifically, EPA is granting the petition under TSCA section 21 to initiate a rulemaking proceeding or issue an order under TSCA section 4(a)(1)(A)(i) compelling health and environmental effects testing regarding PFAS. EPA has determined that the petition sets forth facts demonstrating that it is appropriate to issue a section 4 order to address the health and environmental effects of PFAS. As such, EPA is granting the petition and will exercise its TSCA authorities to compel development of information on PFAS. However, EPA is not making any final determinations in this letter regarding whether the TSCA section 4 criteria have been met with respect to any particular chemical substance. Specific determinations regarding whether the criteria for issuing TSCA section 4 orders have been met will be made when EPA issues such test orders.

As discussed above, once the Agency grants a petition under section 21, the Agency is required to promptly commence an appropriate proceeding. A grant does not, however, commit EPA to issue an order or rule that conforms specifically to the petitioners' suggested proceeding or order. As further described below, EPA will promptly commence an appropriate proceeding in accordance with its statutory authority. In the interest of transparency, this response also describes EPA's current views with respect to the proposed testing program presented in the petition (i.e., testing for 54 individual chemical substances, the animal toxicity testing of certain chemical mixtures, the human studies and human half-life studies, submission of analytical standards, and oversight by the NASEM) and to what extent EPA expects to conform its actions both in substance and in timing to the petitioners' requests as it commences an appropriate proceeding. The Agency believes that the actions it intends to commence will directly address the concerns of the petitioners and will constitute the appropriate proceeding.

A. Expected Actions on the 54 Chemical Substances Identified in the Petition

EPA believes that the best approach under TSCA to understand the health and environmental effects associated with PFAS is to initiate a program to develop information using the authority of section 4 of TSCA. EPA has therefore granted the petition and believes that the prompt issuance of orders under section 4(a)(1)(A)(i) in accordance with the Agency's Testing Strategy is the appropriate response to the proposal that the desired testing be performed on the 54 substances identified by petitioners. EPA acknowledges that the petition and request for reconsideration of the previous denial thereof were integral drivers for advancing the Agency's plans for a comprehensive testing strategy for PFAS.

1. Introduction to the Testing Strategy

As announced on October 18, 2021, EPA’s Office of Chemical Safety and Pollution Prevention (OCSPP) and Office of Research and Development (ORD) have collaborated to develop the Testing Strategy – one of the largest testing programs ever undertaken in the Agency’s history – to deepen understanding of the impacts of PFAS, including potential hazards to human health and the environment (Ref. 2). This Testing Strategy will help EPA identify and select PFAS for which the Agency will require testing using TSCA authorities, and through implementation of the Testing Strategy, EPA expects to gather information on physical-chemical properties, fate and transport, human health effects, and, in the future, environmental health effects relevant to thousands of PFAS that have historically been made or used in the U.S. There are hundreds of PFAS in commerce that have limited or no toxicity data. If EPA attempts to research them one at a time, it will be impossible for EPA, states, or communities to expeditiously understand, let alone address, the risks these substances may pose to human health and the environment. The Agency believes the testing to be conducted under the Testing Strategy, and the category approach it employs, will be a strategic and effective use of limited resources to address this issue, and will also be consistent with statutory direction to utilize a tiered testing approach and reduce testing in vertebrate animals. Additionally, EPA expects that the initial phase of testing will yield information relevant to 30 of the specific 54 chemical substances listed in the petition (Table 1) and will support continued refinement of the Testing Strategy. A more detailed description of the Testing Strategy, including the use of categories and tiered testing, and how the Testing Strategy specifically addresses the 54 petition substances, is provided in subsequent sections.

The Testing Strategy grouped 6,504 PFAS by structural and physical-chemical properties into 70 total terminal categories. Of the 70 terminal categories in the Testing Strategy, three were characterized as ‘data-rich’ with regard to available human-health related toxicity test information and therefore are not a focus for the first phase of testing.³ The remaining 67 of 70 terminal categories are considered ‘data-poor.’ Of these 67 terminal categories, a total of 24 PFAS from 24 different data-poor terminal categories were selected for the first phase of testing (see Testing Strategy for details on selection of the 24 categories for initial testing). Using the category approach, the 24 PFAS selected for phase 1 testing are expected to provide information on the human-health effects of the 2,950 PFAS included in these 24 terminal categories. EPA is reviewing the remaining 43 data-poor categories to determine what testing may be required. Additionally, EPA notes that certain PFAS within the remaining data-poor categories have robust data sets available, which EPA needs time to evaluate prior to determining whether testing may be necessary for these categories.

As described in the Testing Strategy, the Agency identified categories of PFAS for initial testing, in part, by consideration of availability of existing test data on the toxicity of PFAS (both publicly available and submitted to EPA under TSCA). The Agency’s consideration of existing

³ The Agency notes a discrepancy between this explanation of the initial test candidate identification and the explanation in the Testing Strategy. Specifically, the Testing Strategy states that 14 categories were excluded as “data rich” substances, leaving a total of 56 categories as “data poor,” rather than the 67 identified in this response as “data poor.” The change is the result of further analysis and this discrepancy will be reflected in a future version of the Testing Strategy.

toxicity data generally ensures future adherence to the requirements of TSCA section 4, e.g., utilization of a tiered screening and testing process, ensuring that there are insufficient data associated with a category that would necessitate further testing, and reducing vertebrate animal testing. EPA will use the Testing Strategy to identify important gaps in existing data and to select one or more candidate chemicals within identified categories for additional study as appropriate.

The first phase of testing is intended to address some of the highest-priority, human-health-relevant data gaps identified using the structural grouping approach in the Testing Strategy. However, it is just the first phase. In addition to the use of a tiered testing approach to determine the necessity of higher tier testing for a specific PFAS, the Testing Strategy is also intended to include multiple phases. For example, beyond the first human-health-relevant phase of testing, the Agency anticipates that additional testing needs may arise:

- For different endpoints (e.g., ecological vs human health) for the same 24 categories of PFAS;
- For categories of PFAS not included in the first human-health-relevant phase after additional review of existing data and/or identification of additional manufacturers or processors; and
- Following refinement of the Testing Strategy in response to further evaluation of degradation products, exposure data (e.g., environmental monitoring, biomonitoring), additional existing data, and results of earlier tiers/phases of testing.

Therefore, the Testing Strategy should be considered a dynamic and evolving approach to deepen the understanding of the impacts of PFAS, including potential hazards to human health and the environment.

i. Use of Categories

The Agency believes that EPA's Testing Strategy, which relies on a category-based approach, is a scientifically defensible and more appropriate approach to understanding the potential health and environmental effects of PFAS than testing thousands of individual chemicals. It is also consistent with TSCA's encouragement to use such an approach. EPA's Office of Pollution Prevention and Toxics (OPPT) in OCSPP has a long history of using chemical categories in conducting chemical assessments (Ref. 14) and has led the way in championing this approach internationally by contributing substantially to the Organization of Economic Cooperation and Development (OECD)'s *Guidance on Grouping of Chemicals* (Ref. 15). As acknowledged in the OECD guidance, use of categories "was first developed by the US-EPA in support of the US HPV Challenge Program in 1998."

As the OECD guidance document explains:

the term 'grouping' or 'chemical grouping' describes the general approach for considering more than one chemical at the same time. It can include formation of a chemical category or identification of (a) chemical analogue(s) with the aim of filling data gaps as appropriate. The category or the analogue approach makes it possible to extend the use of measured data to similar untested chemicals, and reliable estimates that are adequate for classification and labelling and/or risk assessment can be made without further testing. ... In addition[,] it will increase

the knowledge of the hazard properties of chemicals that may otherwise remain untested and provide for an increased level of protection for human health and the environment.

The 2014 OECD document reflects a long history of use of chemical categories within the OECD Cooperative Chemicals Assessment Programme (formerly the OECD High Production Volume Chemicals Programme), the U.S. High Production Volume (HPV) Challenge Program, the European Union (EU) Existing Substances Programme (replaced by REACH3 in 2009), the EU activity on classification and labelling, Canada's Chemicals Management Plan5 (CMP) and Domestic Substances List (DSL) program, guidance issued under the US HPV Challenge Program, and other EPA programs as well as EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation. It also reflects experience and knowledge captured at OECD expert workshops convened in 2004 and 2011. The category approach taken by EPA in the Testing Strategy is consistent with the concepts and approaches described in the OECD document and as such is a well-founded and widely accepted approach to assessing chemicals.

In addition to the statutory encouragement in TSCA Section 4(h)(1)(B) to use categories when requiring testing, Congress directed the development of a category-based approach for addressing PFAS data gaps in the 2020 National Defense Authorization Act. *See* 15 U.S.C. § 8962. This provision required EPA to develop a process for prioritizing which PFAS or classes of PFAS should be subject to additional research efforts based on potential for human exposure, toxicity, and other available information. In collaboration with the National Toxicology Program (NTP), EPA's ORD developed a risk-based approach for conducting toxicity testing for PFAS to inform human health assessments (Ref. 16). Congress has also clearly signaled support for category-based approaches for actions in other sections of TSCA. Section 26(c) of TSCA states that “[a]ny action authorized or required to be taken by the Administrator under any provision of this Act with respect to chemical substance or mixture may be taken by the Administrator in accordance with that provision with respect to a category of chemical substances or mixtures” 15 U.S.C. § 2625(c)(1). Chemicals may be classified as a category based on, for example, similarities in molecular structure or in physical, chemical, or biological properties, or they are “suitable” in some other way for classification as a category under TSCA. 15 U.S.C. § 2625(c)(2)(A).

Building on the long history of OPPT using category and analogue approaches (Ref. 15), and ORD's research in developing PFAS groupings, ORD and OPPT collaborated to group 6,504 PFAS into 70 categories, based on information about similarities in molecular structure and physical-chemical properties to inform testing under TSCA section 4. This approach to developing PFAS categories is described in the EPA's Testing Strategy (Ref. 2).

Those more data-rich members of a given structural category may inform interpolation or extrapolation to data-poor members of the category. Specifically, leveraging various chemical similarity domains such as structural features, physicochemical properties, and/or biological activity information across different levels of organization (e.g., *in vitro* and *in vivo*) between members of a proposed category may facilitate data gap filling for data-poor members. Systematic comparisons of structure, physicochemical and/or biological properties (i.e., ‘read-

across') between chemicals within a given category may: (1) help refine membership of PFAS within a category, (2) identify potential hazard(s) or health outcome domain(s) and associated dose-response for subsets of PFAS within a category and/or for the category as a whole, and (3) save resources (e.g., animals, funding, time) by supporting decision-based needs without the necessity of performing studies for each data-poor PFAS.

EPA believes the use of categories as the basis for identifying PFAS for which testing should be conducted appropriately addresses the concerns outlined in the petition, is consistent with statutory direction and encouragement of a categorization approach, and furthermore, using EPA's category approach within the Testing Strategy is expected to extend the information collected to far more PFAS than the number of PFAS included in the petition. The reconsideration request submitted by petitioners noted that there are "numerous PFAS with likely human exposure" associated with Chemours beyond the 54 substances identified in the petition. Because the use of categories in the Testing Strategy will facilitate data gap filling for "data-poor" PFAS beyond the petition, the information collected under the Testing Strategy also aims to provide an understanding of such additional PFAS that may be present in the Cape Fear River watershed.

ii. Use of Tiered Testing

The petitioners also recommended a non-tiered approach to evaluating the health and environmental effects of PFAS, meaning that the petitioners requested that EPA require the development of all the proposed studies at the same time. However, TSCA section 4(a)(4) states that when requiring the development of new information under this subsection, the Agency shall employ a tiered screening and testing process, under which the results of screening-level tests or assessments of available information inform the decision as to whether one or more additional tests are necessary, unless information available to the Administrator justifies more advanced testing of potential health or environmental effects or potential exposure without first conducting screening-level testing. The Agency's Testing Strategy will require testing using a tiered approach, with each tier's tests identified in each test order, as required by the law. Although the petition separated the 54 PFAS into two tiers to differentiate the types of tests that the petitioners requested be conducted for each of the substances, that tiering is distinct from what is required under TSCA.

EPA's tiered testing relies on existing data to determine the appropriate testing for each tier, in accordance with statutory requirements. For example, as part of the development of the Testing Strategy, EPA has arrayed different types of tests (e.g., physical-chemical properties, in vitro mechanistic or kinetics testing) into tiers such that the results of tier 1 and 2 tests inform whether and/or how tier 3 tests should be conducted. Based on results of lower tiered testing, EPA will consider systemic toxicity testing that measures adverse endpoints such as liver and kidney disease, immunotoxicity, thyroid function, lipid dysregulation and reproductive and developmental toxicity, consistent with the endpoints of concern identified in the petition.

iii. Reduction of Vertebrate Animal Testing

EPA's Testing Strategy includes a combination of: (1) rigorous searching for reasonably available existing toxicity information both publicly available and submitted to EPA under TSCA, (2) use of chemical categories, (3) tiered testing, and (4) encouraging the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests to meet the mandates and goals of TSCA section 4(h). As such, EPA's Testing Strategy is closely aligned with TSCA section 4(h).

Specifically, TSCA section 4(h) requires that EPA reduce and replace the use of vertebrate animals in the testing of chemical substances and mixtures. Prior to requesting or requiring testing using vertebrate animals, EPA must consider “as appropriate and to the extent practicable and scientifically justified, . . . reasonably available existing information, including - (i) Toxicity information; (ii) Computational toxicology and bioinformatics; and (iii) High-throughput screening methods and the prediction models of those methods.” 15 U.S.C. § 2603(h)(1)(A). As discussed above, the Testing Strategy is consistent with this mandate.

Further, TSCA section 4(h)(2) requires that EPA “promote the development and timely incorporation of new scientifically valid test methods and strategies that are not based on vertebrate animals . . .” 15 U.S.C. § 2603(h)(2). Among the list of examples of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing are: “testing of categories of chemical substances,” “tiered testing methods,” and “industry consortia that develop information submitted under [TSCA],” 15 U.S.C. § 2603(h)(2)(iii), (iv), and (viii), all of which are incorporated into EPA’s Testing Strategy.

2. PFAS Identified in the Petition as Represented in the Testing Strategy Categories

Thirty-nine (39) PFAS identified in the petition are included in the Testing Strategy (see Testing Strategy for inclusion criteria). These 39 PFAS are assigned to 12 of the “data-poor” terminal categories as shown in Table 1. The 12 terminal categories containing the 39 PFAS identified in the petition represent a total of 1,786 of the 6,504 PFAS included in the Testing Strategy.

i. Near-Term Testing Covers 30 of 54 Petition Chemicals

A PFAS identified in the petition has been selected as the representative candidate for the initial phase of testing for seven of the 12 terminal categories containing petition chemicals (marked with an asterisk (*) in Table 1). Six of these seven categories include additional PFAS identified in the petition, such that near-term testing EPA plans to require on the representative PFAS for each of these seven terminal categories will provide information on 21 of the 39 PFAS identified in the petition. For example, the petitioners propose that testing be conducted on perfluoro(4-methyl-3,6-dioxaoct-7-ene)sulfonyl fluoride (CAS No. 16090-14-5), which falls within terminal category “PFAA precursors, less than 8 carbons, cluster 2.” This terminal category includes an additional seven PFAS for which testing is also proposed in the petition. Hence, using a category approach, the testing intended for perfluoro(4-methyl-3,6-dioxaoct-7-ene)sulfonyl fluoride can be extended to the seven additional PFAS identified in the petition and other data-poor chemicals within the terminal category, “PFAA precursors, less than 8 carbons, cluster 2,” for a total of 149 PFAS.

There are an additional four categories that have been selected for the initial phase of testing that contain petition chemicals (marked with two asterisks (**)) in Table 1). For these four categories, the Agency identified the chemical with the most representative structural features for the category (the centroid) as the candidate for the initial phase of testing, although the candidate is not a petition chemical. Near-term testing EPA plans to require on the representative PFAS for each of these four terminal categories will provide information on an additional nine of the 39 PFAS identified in the petition.

Table 1. Summary of the 12 terminal categories containing at least one petition chemicals meeting the OPPT definition of PFAS. PFAS representing 11 of these categories will receive test orders in the initial phase of testing.

National Testing Strategy Terminal Category (Ref. 2)	Number of petition PFAS in the category	Total number of PFAS in the terminal category
PFAAs, less than eight carbons	9	129
PFAA precursors, greater than eight carbons**	6	597
PFAA precursor, less than eight carbons, cluster 1*	3	104
PFAA precursor, less than eight carbons, cluster 2*	8	149
PFAA precursor, volatile, cluster 2**	1	78
Others, greater than eight carbons, cluster 1*	2	230
Others, less than eight carbons, cluster 1, subcluster 2*	1	85
Others volatile cluster 2*	2	175
Others, volatile, cluster 3, subcluster 1*	3	114
Others, cyclic, volatile, cluster 1 *	2	48
Non-PFAA perfluoroalkyls, volatile, cluster 1**	1	45
Non-PFAA perfluoroalkyls, volatile, cluster 2**	1	32
<i>Total</i>	<i>39</i>	<i>1,786</i>
* this category contains one or more PFAS identified in the petition and one of the petition chemicals has been identified as the PFAS for the initial phase of testing for this category; a total of 21 PFAS identified in the petition are included within the categories with a petition PFAS that will be tested.		
** this category contains one or more PFAS identified in the petition; however, the PFAS closest to the centroid, which has been identified as the PFAS for the initial phase of testing for this category, is <i>not</i> a PFAS identified in the petition; a total of nine PFAS identified in the petition are included within these categories with a PFAS that will be tested.		

The initial phase of the Testing Strategy identifies candidates for testing from 11 categories which each contain at least one PFAS identified in the petition and also identifies

candidates from an additional 13 PFAS categories, for a total of 24 PFAS testing candidates representing 24 different “data-poor” terminal categories. These 24 categories include 2,950 PFAS in total, of which 30 are identified in the petition. Thus, the total number of PFAS that will be covered in the 24 initial testing categories is larger than the total number of PFAS in the 12 categories containing petition chemicals (1,786; Table 1). Figure 1 depicts the representation of PFAS identified in the petition within the 70 terminal categories included in the Testing Strategy and the overlap with categories where representative chemicals were selected for phase 1 testing.

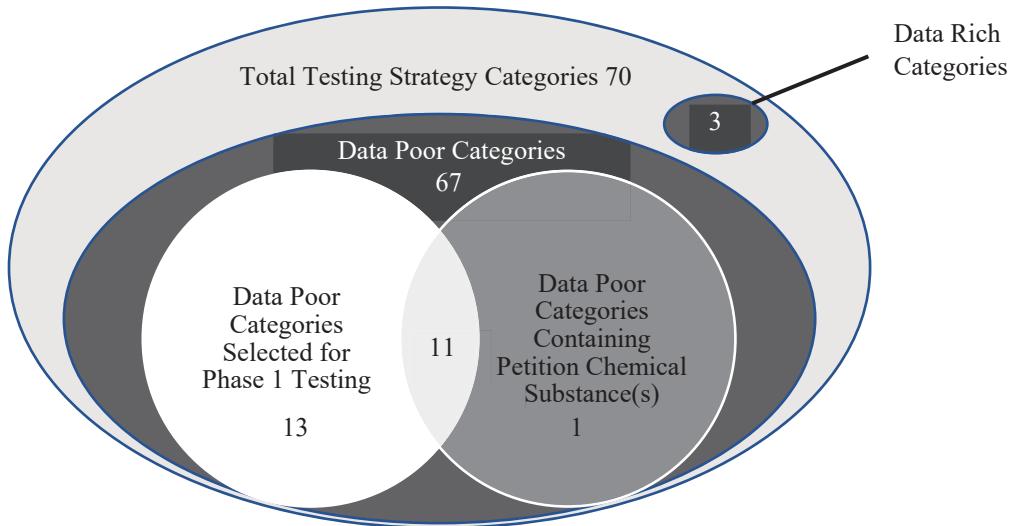


Figure 1: Representation of PFAS identified in the petition within the 70 terminal categories included in the Testing Strategy. The Testing Strategy grouped PFAS by structural and physical-chemical properties into 70 total categories. Three of these categories are characterized as relatively data-rich in regard to available human-health related toxicity test information. From the data-poor terminal categories, 24 categories contain candidate substances selected for phase 1 testing. Eleven of these categories contain at least one petition chemical substance. One additional category contains petition chemical substances and is not currently selected for phase 1 testing but is being reviewed for later consideration.

ii. Subsequent Testing May Cover 9 of the 54 Petition Chemicals

Nine PFAS identified in the petition fall into one “data-poor” category (see Figure 1), “PFAAs, less than eight carbons”, for which a candidate PFAS has not been identified for testing in the first phase of the Testing Strategy (Table 1). The Agency will continue to evaluate the data needs and associated manufacturer information for the chemicals in this category and may require testing on a candidate PFAS in a later phase.

iii. Remaining 15 of 54 Petition Chemicals

Fifteen substances identified in the petition (Table 2) do not meet the definition of “PFAS” for purposes of the Testing Strategy; therefore, the Agency has decided it is not appropriate to require the development of information about these substances at this time. As described in further detail below, the definition was developed to focus the Agency’s testing

efforts on PFAS believed to be of the highest concern. Additionally, several of these 15 chemicals are not ideal candidates for the first phase of testing as they have relatively robust existing toxicity information (superscript *b*; Table 2), or are related to chemicals with relatively robust toxicity information, all of which would limit the Agency's ability to satisfy the section 4 requirements for issuing test orders as proposed by the petitioners at this time.

Table 2: Summary of the 15 chemical substances in petition not addressed through PFAS Testing Strategy because they do not meet the OPPT Working Definition of PFAS.

CAS No.	Chemical Name
39492-90-5	Perfluoro-3,5,7,9-butaoxadecanoic acid
39492-91-6	Perfluoro-3,5,7,9,11-pentaoxadodecanoic acid
39492-88-1 ^a	Perfluoro-3,5-dioxahexanoic acid
39492-89-2	Perfluoro-3,5,7-trioxaoctanoic acid
674-13-5 ^a	Difluoro(perfluoromethoxy)acetic acid
116-14-3 ^b	Tetrafluoroethylene
116-15-4 ^b	1,1,2,3,3,3-Hexafluoro-1-propene
1187-93-5 ^b	Trifluoro(trifluoromethoxy)ethylene
1514-85-8	Difluoromalonic acid
353-50-4 ^b	Carbonic difluoride
354-34-7	Trifluoroacetyl fluoride
422-67-3	Difluorosulfoacetic acid
677-67-8	Difluoro(fluorosulphonyl)acetyl fluoride
69116-71-8	2,2-Difluoro-3-oxopentanoyl fluoride
21703-43-5	1,1,1,3,3,5,5-Heptafluoro-2,4-dioxahexan-6-oyl fluoride

^a Chemical subject to toxicity studies pursuant to Chemours Consent Order
^b Chemical has relatively robust toxicity information available

In the Testing Strategy, EPA applied OPPT's working definition of PFAS (i.e., the chemical contains at least two adjacent carbon atoms, where one carbon is fully fluorinated and the other is at least partially fluorinated), among other structural filters, in developing PFAS categories to inform future testing. This working definition identifies chemicals with at least two adjacent carbon atoms, where one carbon is fully fluorinated and the other is at least partially fluorinated. This EPA/OPPT working definition is focused on substances likely to be present in the environment, especially water, thereby focusing on substances with greater potential for exposures to people/environment and by extension more potential to present risks. For example, chemicals with (-CF₂-) that are not (-CF₃) are expected to degrade in the environment, and most substances with only one terminal carbon (-CF₃) are expected to degrade to trifluoroacetic acid, which is a well-studied substance. This working definition focuses on PFAS believed to be of highest concern based on their persistence and potential for presence in the environment and human exposure.

Although not included in the Testing Strategy, EPA applied the same search procedures described in the Testing Strategy to identify reasonably available, human-health related toxicity studies for these 15 substances. For example, for 1,1,2,3,3,3-hexafluoro-1-propene (CAS No. 116-15-4), EPA identified a number of toxicity studies that are already available including acute, subchronic, chronic, developmental toxicity and reproductive toxicity, mutagenicity, irritation and/or sensitization studies along with biomonitoring data. The results of the Agency's search on carbonic difluoride (CAS No. 353-50-4) are also notable, as it is highly reactive and has numerous acute duration toxicity studies available. Its reactivity also precludes it, for toxicological and logistical reasons, from being tested for longer durations, thus it would not be appropriate to require chronic exposure testing for this chemical.

EPA is undertaking efforts to conduct more in-depth analyses of the existing data for these 15 substances, which will inform later phases of testing.

B. Expected Action with Respect to Testing on Mixtures

Petitioners recommended that the Agency require toxicity testing on three discrete mixtures of PFAS that are alleged to be representative of the PFAS contamination of the communities living near and downstream of the Chemours facility. While the Agency is supportive of developing approaches to evaluate PFAS mixtures, EPA believes that a better understanding of individual PFAS that have been strategically selected to be representative of thousands of PFAS – a goal that would be furthered by the category approach contemplated in EPA's Testing Strategy – will provide the tools to assess many more PFAS mixtures than an immediate focus on a limited few discrete PFAS mixtures that have a finite applicability, i.e., limited to only that specific mixture. Such mixture studies are unlikely to meaningfully capture the interactions between the hundreds of PFAS potentially present in the environment and the range of exposures of the Cape Fear River watershed communities. EPA believes it would be premature to require testing on discrete PFAS mixtures before better understanding the individual component chemicals. Consideration of the information collected under the Testing Strategy will also assist the Agency in its determination of whether effects information on a mixture may *not* "be reasonably and more efficiently determined or predicted" by testing the individual substances in the mixture. 15 U.S.C. § 2603(a)(1)(B).

EPA has existing guidance for conducting health risk assessments of chemical mixtures (Ref. 17, 18), which suggests a hierarchy of hazard and dose-response information for evaluation of mixtures of chemicals. Data associated with whole mixtures (i.e., a specific mixture of interest) are considered optimal, when available, however guidance still recommends consideration of the components in the mixture in response to environmental degradation or in the case of differing endpoints of concern. The diversity of PFAS co-occurring in different component associations and proportions in environmental matrices (e.g., water, soil, air) makes whole mixture testing and evaluations extremely difficult and complex. In the environment, characterization of any given mixture is complicated and typically limited to a particular situation and time due to a number of factors including differing fate and transport properties of chemicals; biotic (metabolism) and abiotic (degradation) processes such as a result of pH, ultraviolet radiation, or media temperature; and PFAS mixtures commonly co-occurring as an array of parent species, metabolites, and/or abiotic degradants. In controlled experimental study

designs, whole mixtures can be assembled with defined component chemical membership and proportions. However, the toxicity associated with exposure to a defined mixture in a laboratory setting is relevant *only for that specific mixture* and may not be relevant or translatable to other PFAS mixtures of different component associations and proportions. Indeed, increasing environmental sampling evidence (e.g., water, air, and soil) suggests that the complexities associated with the diversity of PFAS co-occurring in different mixtures make evaluating each unique whole mixture intractable, which is why component-based mixture approaches (e.g., where the toxicity of the product is predicted from the toxicity of individual components using concentration addition) are considered particularly useful and appropriate for addressing the joint toxicity of multiple (i.e., two or more co-occurring) PFAS.

EPA mixtures guidance provides several options for component-based assessment based on different assumptions of how substances behave chemically and/or biologically in mixtures (Ref. 17, 18). For example, ‘dose addition’ applies when mixture components act on similar biological systems and elicit a common toxic response (section 4.1.1, Ref. 17). In contrast, ‘response addition’ applies when mixture components act on different biological systems or produce effects that do not influence each other (section 4.1.1, Ref. 17). Experimental evidence from mixtures studies across several classes of environmental chemicals (e.g., PCDD/Fs, PAHs, DBPs, phthalates) have supported an assumption of dose additivity (Ref. 19). To date, linear (e.g., PFOA, PFOS) or branched (e.g., GenX chemicals) PFAS have been shown to activate similar cellular receptors (e.g., PPARs, CAR, LXR, PXR) and produce common toxicological effects in multiple tissues, across life stages and species. For example, recent PFAS mixture studies in rodents demonstrated that combinations of PFAS such as PFOA, PFOS, GenX chemicals, and Nafion byproduct 2 induce maternal and fetal health outcomes (e.g., neonatal mortality, decreased pup body weight, alterations in maternal thyroid hormone levels and gestational weight gain) consistent with dose addition (Ref. 20, 21, 22). EPA component-based mixtures risk assessment methods based on dose addition, such as the hazard index and relative potency factor, have been suggested in the evaluation of same/similar non-cancer health effects associated with co-occurring PFAS in water (Ref. 23). The same dose addition-based mixtures assessment approaches may inform component-based evaluation of PFAS under the context of the Testing Strategy as well.

For example, the EPA’s Office of Water (OW) and ORD recently co-authored a *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)*, which is under review by EPA’s Science Advisory Board (SAB). Further, the EPA’s Risk Assessment Forum is coordinating the finalization of a report designed to advance the science of dose additive approaches in chemical mixtures assessment. Importantly, the data objectives and application foci presented in this report are consistent with multiple EPA efforts summarized here and is indicative of close coordination between OCSPP and the rest of the Agency on a comprehensive approach to further the science and research needed to address risks from PFAS, including mixtures of PFAS.

Considering the complexity of potential combinations of PFAS components in environmental mixtures, and the diverse array of bioactivity and toxicity information for individual PFAS, it is logical to anticipate a mixed profile of PFAS additivity. This aspect is a key consideration inherent in the proposed category-based approach. That is, assigning

structurally-diverse PFAS to categories or subcategories is an essential starting point for subsequent evaluations of potential additivity (or deviations from additivity, such as synergistic or antagonistic interactions). A reasonable default assumption for members of a given category is that they would induce a mixture effect via dose additivity. However, if toxicity testing evidence suggests a mix of dose and response addition across members of a category, existing EPA guidance includes methods (e.g., Cumulative Relative Potency Factors) to facilitate analysis of PFAS both within a category and across categories as needed and EPA will adjust its approach at that time.

Based on the current state-of-science, continuing to evaluate the progress of ongoing PFAS mixture studies and methodologies is also squarely consistent with the TSCA section 4 statutory requirement that EPA require the development of information about mixtures only when the effects of the mixture “may not be reasonably and more efficiently determined or predicted by testing the chemical substances which comprise the mixture.” 15 U.S.C. § 2603(a)(1)(B).

C. Expected and Ongoing Actions with Respect to Human Studies

Petitioners also suggested, as part of the proposed testing program, that EPA compel Chemours to conduct a human epidemiological research study specifically of Cape Fear River watershed residents. Considering the multiple ongoing nationwide efforts to address community PFAS exposures and the significant resources it would take for EPA to initiate such a study, the Agency currently believes it is both appropriate and consistent with EPA’s statutory obligations to continue to engage and partner with existing ongoing research efforts related to PFAS health studies that will help characterize potential health and environmental effects from PFAS in Cape Fear River watershed communities and is considering additional opportunities to further support these efforts. As discussed in greater detail below, multiple epidemiological studies are ongoing, both by EPA and other federal partners, and EPA intends to consult and cooperate with its federal partners, e.g., Centers for Disease Control (CDC) and the NIEHS, to continue to evaluate how ongoing research will directly inform this issue. Such coordination is consistent with TSCA section 9(d), which additionally provides that the EPA Administrator shall consult and cooperate with other Federal agencies “for the purpose of achieving the maximum enforcement of [TSCA] while imposing the least burdens of duplicative requirements” on those subject to TSCA. 15 U.S.C. § 2608(d). EPA intends to consider the information developed through these efforts to determine whether it is appropriate to require the development of additional epidemiological information under TSCA section 4.

1. Ongoing Human Studies at the CDC

CDC’s Agency for Toxic Substances and Disease Registry (ATSDR) is conducting a cross-sectional multi-site study to evaluate potential associations between measured and historically reconstructed serum levels of PFAS and selected health outcomes in communities whose drinking water was impacted by PFAS (Multi-site Study). Contrary to the petitioners’ claim that the ATSDR studies are limited to military sites and aqueous film-forming foam (AFFF) (Ref. 8), EPA has confirmed with ATSDR that the human studies included in the Multi-Site Study include sites with drinking water impacted by both AFFF use at military bases and

PFAS emissions from commercial/industrial facilities. ATSDR is conducting a pilot study site around the Pease Airport near Portsmouth, NH, as well as funding seven additional health studies with academic partners around the country (CO, MI, PA, NJ, MA, NY, and CA) to study cohorts near both industrial sites and military bases. This ATSDR sponsored Multi-Site Study examines each of the health outcomes proposed for study in the petition. ATSDR is also positioning itself to perform additional follow-up and longitudinal analysis of these cohorts (Ref. 24). For these reasons, EPA believes the ATSDR Multi-site Study will inform the health outcomes associated with past and current exposures in residents exposed to PFAS in drinking water for all communities in the U.S., including those exposed to PFAS in drinking water from the Cape Fear River.

CDC is conducting several additional studies on the health effects of PFAS. This includes two ecologic studies (i.e., comparisons of groups rather than individuals) to examine aggregate-level incidence rates of various health outcomes (collected from state vital statistics and cancer registries) related to geographically-defined levels of PFAS in drinking water (measured via EPA's Unregulated Contaminant Monitoring Rule 3 (77 FR 26072) (FRL-2012-9978)). CDC is also collaborating with the American Cancer Society to examine the association between serum PFAS levels and subsequent development of cancer of several types (cancers of the kidney, bladder, breast, prostate, pancreas; and hematopoietic malignancies). EPA believes these ongoing CDC studies evaluating the health effects associated with drinking water exposures to PFAS will also inform the health outcomes associated with past and current exposures in residents exposed to PFAS in drinking water all communities in the U.S., including those exposed to PFAS in drinking water from the Cape Fear River.

2. Ongoing Human Studies at EPA

EPA is also evaluating how to leverage existing ongoing epidemiological research efforts related to PFAS and how to promote novel research efforts (e.g., familiarity with possible cohorts), as appropriate, to address the PFAS issue in a broader context than the efforts noted above.

For example, EPA's own *Multimorbidity and PFAS Exposure in an Electronic Record Cohort* study is using electronic health records in North Carolina (10,168) to evaluate multimorbidity (two or more chronic diseases) via logistic regression and cumulative link models adjusted for age, race, sex, smoking, socioeconomic status, health care access and food availability (Ref. 25). The results thus far of this effort indicate exposure to PFAS is associated with multimorbidity in this cohort and associations for both PFOA and PFHpA are consistent and robust to various adjustments.

EPA is also collaborating with research partners by providing technical support and environmental data. EPA's collaborations with ATSDR include follow up site assessments to better characterize a broad array of exposures (Ref. 24). EPA also has additional ORD grants for work on PFAS, and the intent of the grants is to advance PFAS human exposure measurement methodologies and encourage common collection of concordant information that will increase impact of individual studies and enable understanding of the most important PFAS exposure pathways (Ref. 26). EPA is also collaborating with NIEHS on their PFAS research program (Ref. 27). Specifically, EPA's ORD developed a risk-based approach for conducting toxicity

testing for PFAS to inform human health assessments with the National Toxicology Program (NTP) and screen more than 100 PFAS to identify common and overlapping patterns of toxicity (Ref. 16).

3. Ongoing Human Studies by North Carolina State University Center for Environmental and Human Health Effects of PFAS

The NC State Center for Environmental and Human Health Effects of PFAS is also specifically studying PFAS exposures and health outcomes in the Cape Fear River region (Ref. 28). The mission of this center is to advance research, technology development, training, and community engagement about exposure to PFAS. The stated long-term objectives are to assess: (1) PFAS exposure in impacted areas; (2) PFAS toxicity and underlying mechanisms of thyroid and immune function; (3) PFAS bioaccumulation potential; and (4) PFAS remediation. A notable recent effort is the GenX Exposure Study (Ref. 28), which is a five-year prospective epidemiology study of approximately 1,200 people in the Cape Fear River region. Petitioners have expressed concern in their letter on July 28, 2021 about the study's funding limitations and narrow focus on thyroid health endpoints (Ref. 8). However, EPA has learned the GenX Exposure Study was additionally funded to review immunological endpoints related to COVID-19, including looking at the prevalence of overt disease, symptoms, sequelae, and antibodies in this population and investigating whether PFAS exposure modifies the response to the virus as measured by antibodies (Ref. 29). Both thyroid and immunological endpoints were cited as health endpoints of particular interest in the petition. These ongoing human studies are directly relevant to communities potentially exposed to PFAS in drinking water in the Cape Fear River region.

4. Limitations at EPA for Designing and Conducting Human Studies

EPA agrees with the petitioners that human surveillance data collected in epidemiological research has significant utility in better understanding the potential exposures to PFAS, as well as the associated health effects of PFAS on impacted populations. However, EPA believes that there are significant challenges to issuing an order for the type of study contemplated by the petitioners, and these challenges further support why the Agency believes it is not appropriate to compel such a study at this time.

Petitioners argue that the Agency could “quickly design” a test order. This is not the case. Such a study would be costly, complex, and difficult for the Agency to properly execute. For example, Kabat’s work related to the Long Island Breast Cancer Study recommends caution related to issues such as initial study design and thoughtful consideration of the underpinning exposure metrics used to define the scope of such research (e.g., selection of chemicals to be evaluated) (Ref. 30). If epidemiological research was required in a test order, it could take years to develop and a significant level of Agency resources to initiate such a study since a broadly accepted protocol and guideline for regulatory purposes does not exist at this point in time. The Agency would not merely draw from the West Virginia C8 study, as suggested, in order to develop such a protocol under TSCA. Issues such as development of a protocol, public involvement, peer review of a study design, recruiting practices, and oversight of the study would need to be addressed. Also, the Agency would need to consider the Federal Common Rule

for protection of humans in research (Ref. 31) and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Ref. 32). Given these considerations, it is likely that planning and initiation of a high quality de novo epidemiological study would take multiple years. For example, for the Agricultural Health Study (AHS), a large complex effort focused on pesticide users, recruitment for participants in the study alone was a multi-year process in a focused, geographically-limited population (e.g., pesticide users in Iowa) (Ref. 33).

D. Expected Action with Respect to a Human Half-Life Study

The petitioners also proposed that EPA compel Chemours to conduct “longitudinal studies” of its workers to measure “the rate of increase and rate of decay of serum or tissue levels as exposure begins or ceases in order to determine half lives in humans.” Based on the wording in the petition, the Agency believes the petitioners could be referring to either a biomonitoring study of Chemours workers or an examination of biokinetic parameters for an array of PFAS chemicals in human subjects. At this time, EPA believes it is appropriate to defer any actions to further characterize the half-lives of PFAS in humans because the results of the animal studies included in the initial test orders will inform the design of such human studies and, as described in further detail below, there are both existing studies and ongoing research efforts that will inform the Agency’s deliberations on whether and which additional tests are necessary. Thus, EPA intends to consider the information developed through these efforts to determine whether it is appropriate to require the development of additional information under TSCA section 4.

If the petitioners are referring to an examination of biokinetic parameters for the 54 chemical substances in human subjects, EPA agrees that biokinetic parameters are important for further evaluation of exposure, dose, and toxicity, but is deferring acting on this proposal at this time in order to gather information under the Testing Strategy that is a necessary precursor to any examination of biokinetic parameters in humans. *See* 15 U.S.C. § 2603(a)(4). The petitioners use the term, “rate of decay,” which is particular to radioactive decay; EPA believes the more general term “rate of elimination” is more appropriate. Elimination may have first order or non-first order kinetics, depending on the mechanism(s) by which a substance is removed from the systemic circulation. First order elimination presumes there is a “half-life” that is constant and can be measured. In fact, there is evidence for some PFAS that elimination may in part be due to active transport in the kidneys, which would indicate the kinetics are non-first order (Ref. 34). The tiered testing outlined in EPA’s Testing Strategy would be fundamental for designing an effective and appropriate human biokinetic study of poorly characterized chemicals. For example, the testing will establish key parameters, such as whether elimination occurs via first or second order kinetics, whether the kinetic processes are saturable in the body, and what are the key mechanisms of elimination. Hence, the design and utility of human studies would be better informed by collection of more fundamental data. The collection of key parameter data will also improve the potential extrapolation of limited human data, as was the case in EPA’s recently issued PFBS toxicity assessment (Ref. 35). As EPA proceeds with the Testing Strategy, the Agency will evaluate the appropriateness of requiring the development of human half-life studies.

If petitioners are referring to a biomonitoring study of Chemours workers for the chemicals that are more well characterized, Chemours has already completed such a study for

GenX and submitted the results to EPA, which are available in ChemView (Ref. 36). EPA is also aware of similar studies available on other PFAS, and the proposed TSCA section 8(a)(7) rule would also require the submission of all “existing environmental and health effects information,” which could include existing biomonitoring studies for PFAS. ATSDR’s Multi-site Study, discussed further above, is also potentially relevant to petitioners on this issue as the study is reconstructing historic serum concentrations for measured PFAS by estimating half-lives and elimination rates, as well as water contamination modeling to inform the pharmacokinetic parameters and modeling. The study will also evaluate changes in PFAS concentration over time at sites that have existing PFAS biomonitoring.

The significant challenges for ordering human subject studies described above in the response on human epidemiologic research would also be relevant for a human biomonitoring study, and there are additional challenges raised by the proposed study as it is described in the petition. Under TSCA section 4, before requiring “epidemiologic studies of employees,” EPA must consult with the Director of the National Institute for Occupational Safety and Health. 15 U.S.C. § 2603(b)(2)(A). In addition, the inclusion of “tissue level” monitoring to evaluate biokinetics is highly invasive and would necessitate the collection of biopsies, which in turn would require a highly detailed justification to an Institutional Review Board in order to be approved (Ref. 31). For example, the petitioners did not specify which tissues should be included in the proposed monitoring or why this is critical information that could not be obtained via less invasive means (e.g., serum or urine samples).

E. Expected Action with Respect to PFAS Analytical Standards

The petitioners also proposed that the Agency require the development and submission of analytical standards for the 54 chemicals identified in the petition under section 4(a)(1)(A)(i). The petitioners specifically refer to EPA method OPPTS 860.1650 as the appropriate test guideline, which is the test guideline for submittal of analytical reference standards (Ref. 37). EPA understands analytical standards to mean reference chemical materials used to calibrate and quantitate specific substances (i.e., physical samples of the chemical substance).

To the extent the petitioners seek issuance of a rule or order under TSCA section 4(a)(1)(A)(i) for the development and submission of analytical standards, the Agency does not have the authority to take such action. Under section 4(a)(1) of TSCA, the Administrator shall require “testing be conducted on” a substance. 15 U.S.C. § 2603(a)(1). This provision does not cover the development of physical samples of a chemical substance or mixture; therefore, the Agency cannot issue a rule or order for the development of an analytical standard under section 4(a)(1)(A)(i).

However, the Agency may order submission of an analytical standard as part of the protocol and methodology for a larger test rule, order, or consent agreement if this were deemed necessary to assure that the information developed under the required test were reliable and adequate. See 15 U.S.C. §§ 2603(b)(1)(B) and 2602(15)(B)(iii). The Agency does not believe it is appropriate at this time, however, to require the submission of analytical standards as part of the test orders issued under the Testing Strategy. EPA’s experience in handling PFAS in procuring and storing samples for more than 400 PFAS from commercial suppliers for use in

research indicates there can be significant storage, sample stability, and resource constraints to collecting and preserving analytical standards. Even under standard -20 degree storage conditions, EPA has observed significant degradation of ~15% of neat samples over the course of weeks and months making the samples unweighable (and therefore unusable), particularly for many lower molecular weight PFAS of interest with fewer than 8 perfluorinated carbons. EPA does not believe it is otherwise necessary to request such standards in conjunction with the first phase of testing to assure that information received is reliable or adequate.

Although the petitioners clearly recommend use of the guideline study for the development of analytical standards, the petitioners also refer to the development of “analytical tools for detecting and measuring the presence” of PFAS in the environment. The use of this language could be interpreted to refer to the development of “analytical methods,” which EPA understands to mean the procedures used to measure the amount of particular contaminants in various types of media samples (Ref. 38). Analytical methods generally describe how to collect, preserve, and store the sample; gather, separate, identify, and measure contaminants in the sample; meet quality control criteria; and report the results of the analysis. The Agency has solicited public comment in the proposed TSCA section 8(a)(7) reporting rule on whether to require the submission of existing analytical methods for PFAS as a data element under the rule. (86 FR 33926, 33934) (FRL-10017-78) (June 26, 2021). EPA plans to address this issue as a part of that rulemaking.

F. Expected Action with Respect to Oversight by National Academies of Sciences, Engineering, and Medicine and/or the Science Advisory Committee on Chemicals

The petitioners also propose that the National Academy of Sciences (now known as the NASEM) oversee all aspects of their proposed testing program. EPA finds such an oversight arrangement is not within the scope of what a TSCA section 21 petitioner can request when seeking the initiation of a rule or the issuance of an order under TSCA section 4; therefore, the Agency has no obligation to grant or deny this request. EPA is not in a position to require NASEM to oversee the testing proposed by the petitioners, and the petitioners provide no administrative or organizational procedures for implementation.

In its request to reconsider, petitioners identify the Science Advisory Committee on Chemicals (SACC) as an alternative entity to the NASEM to serve in an oversight role. EPA finds such an oversight arrangement is not within the scope of what a TSCA section 21 petitioner can request when seeking the initiation of a rule or the issuance of an order under TSCA section 4. The Agency does not believe it is appropriate to ask for SACC review of the Testing Strategy at this time.

IV. Conclusion

As previously stated, after review of the petition, the reconsideration request, and the subsequent letters submitted by petitioners and others, the Agency has determined to grant the petition. EPA will promptly commence an appropriate proceeding in accordance with the statutory requirement of TSCA section 21. The Agency looks forward to further engaging with

both the petitioners and the public more broadly as EPA works to advance the shared goals of better understanding and addressing the risks of PFAS, including those that may be present in the Cape Fear River watershed.

Sincerely,

MICHAL
FREEDHOFF

Digital signature of Michal Freedhoff
Digitally signed by MICHAL
FREEDHOFF
Date: 2021.12.28 12:55:20
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Michal Freedhoff, Ph.D.
Assistant Administrator

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